Received: 20 August 2020 | Revised: 26 November 2020 | Accepted: 17 December 2020

DOI: 10.1111/exd.14267

Experimental Dermatology WILEY

VIEWPOINT

Could basement membrane alterations, resembling micro-wounds at the dermo-epidermal junction in psoriatic non-lesional skin, make the skin susceptible to lesion formation?

Renáta Bozó[1,2] | Lili Borbála Flink[1] | Nóra Belső[1,2] | Barbara Gubán[1] | Márta Széll[3,4] | Lajos Kemény[1,2,3] | Zsuzsanna Bata-Csörgő[1,2,3]

[1]Department of Dermatology and Allergology, University of Szeged, Szeged, Hungary

[2]HCEMM-SZTE Skin Research Group, Szeged, Hungary

[3]MTA-SZTE Dermatological Research Group, Szeged, Hungary

[4]Department of Medical Genetics, University of Szeged, Szeged, Hungary

Correspondence
Renáta Bozó, Department of Dermatology and Allergology, University of Szeged, Korányi Fasor 6, Szeged, H-6720 Hungary.
Email: bozo.renata@med.u-szeged.hu

Funding information
The project has received funding from the EU's Horizon 2020 research and innovation programme under grant agreement No. 739593 and from National Research, Development and Innovation Office, Hungary (Hungarian Scientific Research Fund, NKFIH K135084, K111885 and K128736). RB was supported by the ÚNKP-19-3-SZTE-30 of New National Excellence Program of the Ministry for Innovation and Technology.

Abstract

Current data suggest that tissue microenvironment control immune functions. Therefore, understanding the tissue environment in which immune activation occurs will enhance our capability to interfere with abnormal immune pathology. Here, we argue that studying the constitutively abnormal functions of clinically uninvolved psoriatic skin in patients with plaque type psoriasis is very important to better understand psoriasis pathobiology, because non-lesional skin provides the tissue environment in which the psoriatic lesion develops. A key question in psoriasis is what initiates the abnormal, uncontrolled immune activation in the first place and the answer may lie in the skin. In light of this concept, we summarize abnormalities at the dermal-epidermal junction region which shows a special "non-healing-like" micro-wound phenotype in the psoriatic non-lesional skin that may act as a crucial susceptibility factor in the development of the disease.

KEYWORDS
basement membrane, dermal-epidermal junction, non-lesional skin, psoriasis, wound healing

1 | INTRODUCTION

Psoriasis is a complex inflammatory skin disease, which is mainly characterized by keratinocyte hyperproliferation and massive immune cell infiltration, primarily affecting the skin[1] with a wide-ranging clinical presentation.[2] However, not only the skin can show differences between patients, but some patients have arthritis[3,4] while others may have psoriasis-related other organ involvements.[5] Risk in developing the disease is based on multiple genetic and environmental factors which differ in individuals and in different populations.[6] Pustular psoriasis, the acute systemic generalized form, the chronic localized palmoplantar pustulosis and the acrodermatitis continua of Hallopeau represent a distinct group and have been linked to interleukin (IL)-36 receptor antagonist (IL36RN) mutations. Mutations were also found in that group in a gene encoding the adaptor protein 1 complex subunit (AP-1 complex subunit sigma-3, AP1S3) and a keratinocyte nuclear factor κB adaptor protein (the caspase recruitment domain-containing protein 14, CARD14).[7] Guttate psoriasis is

associated with streptococcal pharyngitis and HLA-Cw6, the most strongly associated psoriasis susceptibility allele.[8] Psoriasis studies, including our own studies, usually focus on the most frequent, dominant plaque type psoriasis phenotype. An inherently abnormal immune regulation, both in innate as well as in adaptive responses, undoubtedly plays a central role in disease pathogenesis.[9] However, it is also clear that the immune pathology is strongly influenced by the tissue environment.[10,11]

An increasing body of evidence suggests that not only the lesional skin of patients is affected in psoriasis, but the seemingly healthy-looking non-lesional skin of patients contains disease-specific alterations as well. In 1995, Kadunce and Krueger suggested that in psoriasis the entire skin has the capacity to develop lesions, and control of expression is linked to a complex interaction of epidermal, dermal and immune cells. They considered psoriatic keratinocytes to have an inherent capacity for hyperproliferation and aberrant differentiation and advised to consider not only cytokines and growth factors, but also regulators of transcription, translation and modifications of cytokines and growth factors.[12] Data suggest that the psoriatic non-lesional skin could represent an intermediate stage between the healthy and lesional skin. Alterations in the non-lesional skin can reveal predisposing factors for lesion development and specific structural changes, or factors which help in the maintenance of the non-lesional stage.[13]

2 | INFLAMMATION IN THE NON-LESIONAL PSORIATIC SKIN

The number of several immune cell types are elevated in non-lesional skin, and the inducible T-cell co-stimulator, ICOS, a T-cell activation marker, is also detected.[14] The characteristically sharp edges of psoriatic plaques are indicative of a very local, tissue-, if not cell-dependent effect. Cytokine signalling plays a key role in the pathomechanism of psoriasis. In psoriatic plaques, Th17 cytokines (mainly the IL-17A) stimulate the production of antimicrobial peptides which activate inflammatory cells, thus sustaining the inflamed state in the psoriatic skin. A large-scale study highlights the psoriasis specificity of IL-17A signature, the importance of cathelicidin (LL37) and an increase in foetal and other protein abundance, suggesting degradation deficiency.[15] The presence of circulating LL37-specific T cells significantly correlates with disease activity.[16] Dermal $CD3^{+}\gamma\delta$ T cells are the major source of IL-17A, and their number is increased in psoriatic skin.[17–19] Meta-analysis on three gene array studies showed enhanced expression of IL-17 and IL-17 signature genes in non-lesional epidermis compared with normal. The transcription factor C/EBPδ also showed elevated expression[14] and it is believed to mediate the IL-17 signalling and it could enhance the sensitivity of non-lesional keratinocytes to IL-17 stimuli.[20] Elevated expression of IL-22 in non-lesional versus healthy skin is associated with an upregulation of antimicrobial peptides.[14] In psoriasis, interferon-γ (IFNγ) is known to take part in the immune induction of the keratinocyte cell cycle progression.[21] In the above-mentioned gene array, the expression level of IFNγ and the IFNγ-related genes also showed higher expression in non-lesional versus healthy skin. It is also interesting to note that some genes, which are known to mediate keratinocyte differentiation processes, are also upregulated in the non-lesional skin.[14] Furthermore, proinflammatory mediators, namely IL-1α and IL-1β, have been reported to show lower expression level in non-lesional skin.[22] According to a recent study, in the clinically resolved lesions epidermal tissue, resident memory T cells are retained in the tissue and can produce cytokines indicating a site-specific T cell–driven disease memory.[23] Besides alterations in the resolved psoriatic skin, epidermal resident T cells in never-lesional skin from patients with psoriasis can trigger psoriasiform tissue responses.[24] These changes in the non-lesional skin affect the professional and non-professional immune cells, and the expression levels of the different cytokines suggest an altered inflammatory state of the clinically asymptomatic skin.

3 | SIGNS OF TISSUE STRESS IN PSORIATIC NON-LESIONAL SKIN

One of the first indications of the altered stress response of the non-lesional skin is the Koebner phenomenon, which means that psoriatic lesions can develop on non-lesional skin after various injuries.[25] Tape stripping is one standard method to induce mechanical stress on the epidermis which results in enhanced proliferation rate [26] and overexpression of transforming growth factor (TGF) alpha in the non-lesional vs. healthy epidermis.[27]

Previously, we compared the expression profiles of non-lesional psoriatic and healthy epidermis, and we identified a long non-coding RNA induced by stress which we named Psoriasis Susceptibility-Related RNA gene induced by stress (PRINS). In our studies, tissue samples are taken from the trunk of healthy and plaque type psoriatic individuals. Interestingly, PRINS is highly expressed in non-lesional psoriatic tissue, but not in healthy or psoriatic lesional epidermis.[28] Later it was shown that PRINS can downregulate inflammation due to destabilization of IL-6 and the chemokine ligand 5 (CCL-5, RANTES) messenger RNAs.[29] Moreover, PRINS can act as an apoptotic function regulator by influencing interferon alpha inducible protein 6 (G1P3) gene expression[30] and by interacting with miR-491-5p[31] and nucleophosmin.[32] Our data indicated that similar to other known stress induced factors,[33] PRINS had a protective effect on cells. Enhanced PRINS production by non-lesional keratinocytes can alter the stress response of the non-lesional epidermis thereby contributing to the pathogenesis of psoriasis.[34]

Further evidence that demonstrates the altered stress/inflammatory state of the non-lesional skin is the elevated expression of the psoriasis-associated danger signal induced caspase recruitment domain family member 18 (CARD18), which has a negative role in keratinocyte inflammatory signalling.[35] Bioinformatic comparison of the gene expression profile of psoriatic non-lesional and healthy epidermis exposed to the same lymphokines suggested altered regulation of cell morphology, development, cell death and

metabolism of small molecules and lipids in psoriatic non-lesional epidermis. Data suggest that differential regulation of IL-23A and IL-1β genes in keratinocytes of psoriatic patients are important in lesion development.[36]

4 | ABNORMALITIES AT THE DERMAL-EPIDERMAL JUNCTION (DEJ) REGION OF PSORIATIC NON-LESIONAL SKIN

Cell-cell and cell-extracellular matrix contact abnormalities, such as the basement membrane (BM) abnormality at the DEJ, can result in cell-extrinsic stress and defense responses, that is a tissue level response, and although it involves innate immune responses, it is not equivalent to the classical acute inflammatory response (para-inflammation).[37] Para-inflammation is an adaptive response to stress and malfunction in tissues that develops for restoration of homeostasis. It is an innate response that can evolve into classic inflammation due to additional or persistent stress or malfunction. Para-inflammation relies mainly on tissue resident macrophages, and indeed activated macrophages was observed in non-lesional psoriatic tissue.[38]

Altered integrin-mediated adhesion of psoriatic keratinocytes can be seen not only in the lesional but also in non-lesional skin. The polarized distribution of α2β1, α3β1 and α6β4 integrins is lost, the β1 integrin subunit is localized to the basal surface of basal keratinocytes and is in contact with the BM, while β4 integrin is detected all around basal and suprabasal keratinocytes.[39] Furthermore, keratinocytes in non-lesional epidermis overexpress the main fibronectin (FN) receptor α5β1 integrin compared with normal skin.[39,40]

In the BM of non-lesional psoriatic skin, discontinuous and uneven laminin-1 distribution was observed.[41] Compared with normal skin, both non-lesional and lesional skin lack the expression of laminin-α1 and there is evidence that without α-chain, there is no distinct BM formation.[42] In another study, gaps, folding and reduplication were described with collagen type-IV α1, α2 chains and laminin-α2, α5, β1 and γ1-chains.[43] A synthetic C16 peptide (KAFDITYVRLKF) that deputizes the functional domain of the laminin-γ1-chain was shown to have an anti-inflammatory effect, including leucocyte infiltration reduction, in a rat acute allergic encephalomyelitis model suggesting an important role of the BM proteins in inflammation.[44]

Two major forms of FN exist, a soluble, found in the serum and synthetized by hepatocytes, and the so-called cellular form, synthetized by fibroblasts, epithelial cells and others.[45] We found that as opposed to normal skin, in psoriatic non-lesional skin, there was serum FN present around basal keratinocytes, which could be explained by a leaky BM.[40] In vivo, the alternatively spliced, extra domain A containing FN (EDA$^+$FN) variant is poorly expressed in adult tissue; however, it is overexpressed in developing embryos, in tumors (it is also called oncofoetal fibronectin), and in highly proliferating tissues, such as wounds. The exact regulation of EDA$^+$FN splicing is not completely clear, but TGFβ1 is known to enhance EDA$^+$FN production in wounded tissue.[46] We have evidence that keratinocytes are able to produce FN and its EDA$^+$ isoform, and psoriatic non-lesional keratinocytes are more readily capable of EDA$^+$FN production in response to signals of activation compared with normal cells.[47] We recently also reported that signal transducer and activator of transcription 1 (STAT1) negatively regulate both FN and EDA$^+$FN expression in healthy fibroblasts and this regulation is compromised in fibroblasts derived from non-lesional psoriatic dermis. We observed that in the non-lesional skin, STAT1 activation was absent in tissues far away from lesions.[48] This is in line with known alterations of psoriatic keratinocytes in the IFN—interferon regulatory factor-1—STAT1—suppressor of cytokine signalling-1 regulatory pathway.[49,50] Recombinant EDA$^+$FN, but not other recombinant FN domains, is known to activate human Toll-like receptor-4 (TLR4) in human embryonic kidney 293 cells. EDA stimulation of TLR4 was dependent upon co-expression of MD-2, a TLR4 accessory protein.[51] This indicates a mechanism by which EDA-containing FN fragments promote an innate inflammatory response.

At the DEJ, α5β1 integrin can mediate FN-mediated proliferative signals and can help in the cell adhesion process as well.[39,50] In addition, together with EDA$^+$FN, α5β1 integrin is overexpressed by basal keratinocytes, when the BM is disrupted, for example at psoriatic non-lesional skin sites or in wounds[52] and binding of α5β1 integrin to EDA$^+$FN is a provisional anchoring mechanism.[53] The recently discovered short laminin peptide C16, representing the laminin-γ1 functional domain, targets the α5β1 integrin and could block the association of α5β1 integrin to FN, thus suppressing FN-mediated proliferative, cytoskeletal, and inflammatory responses in HaCat keratinocytes. Furthermore, in imiquimod-induced psoriasis-like mouse model, C16 could reduce epidermal hyperproliferation and immune cell infiltration.[44]

Recent evidence indicates further abnormalities at the DEJ in psoriatic non-lesional skin suggesting a key role of this site in the pathomechanism of psoriasis. We have previously described that the cartilage oligomeric matrix protein (COMP) is also overexpressed in the psoriatic non-lesional skin.[54] COMP is a structural component of the healthy skin, and it provides the cohesion between the anchoring plaques of the upper dermis and the BM.[55] We found that COMP formed a continuous layer below basal keratinocytes in non-lesional skin and could interact with the α5β1 integrin and EDA$^+$FN due to the disrupted distribution of the laminin-α1. In addition, COMP helps in the maintenance of the non-lesional state by suppressing the proliferation of keratinocytes via interaction with α5β1 integrin despite the overexpression of EDA$^+$FN. COMP may also be involved in influencing keratinocyte proliferation through its direct interaction with EDA$^+$FN.[54]

Matrix metalloproteinases (MMPs) play an important role in the stability and homeostasis of the extracellular matrix (ECM).[56] MMP-2 has the ability to modify the ECM and the BM, as it contributes to cell migration and tissue remodelling and has several substrates including type IV collagen, laminin-1 and FN.[57,58] Both MMP-2 and tissue inhibitor of matrix metalloproteinases (TIMP)-2 are elevated in non-lesional psoriatic skin.[59] MMP-9 also showed higher expression in non-lesional versus healthy skin,[14] and it shares similar functions with MMP-2.[56]

5 | PSORIATIC NON-LESIONAL SKIN EXHIBITS CHANGES THAT RESEMBLE WOUND HEALING

Several studies have provided evidence that psoriasis demonstrates many characteristics of wound repair. Both lesional and non-lesional skin of individuals with psoriasis show significantly faster healing than skin of healthy individuals.[60] Hyperproliferation of keratinocytes, infiltration of inflammatory cells and neovascularization are common processes both in wound repair and in psoriasis. Further similarities are in filaggrin, transglutaminase and involucrin expression in both conditions. Antimicrobial peptides and specifically the antimicrobial protein REG3A, which is largely responsible for keratinocyte proliferation and differentiation after skin injury, are expressed not only following skin injury, but also in psoriasis.[61] Keratin-1 and keratin-10 show reduced, while keratin-6 and keratin-16 show increased expression in both conditions.[62]

Mechanisms similar to the wound healing process can also be observed in the psoriatic non-lesional skin. The EDA^+FN and its receptor, the $\alpha5\beta1$ integrin, is overexpressed not only in psoriasis, but also in wounded tissue.[63–65] The level of COMP in normal healing wounds is minimal; however, in chronic non-healing wounds, such as venous leg ulcer, it is overexpressed,[66] similar to its overexpression in non-lesional skin. High dose recombinant human COMP protein treatment results in a delay in the wound healing in an *ex vivo* wound healing model.[54] The BM is also affected in regeneration of the tissue following injury.[67] In the wound bed, the BM is often not intact, similar to areas of non-lesional skin where the laminin layer within the BM is discontinuous and the EDA^+FN, $\alpha5\beta1$ integrin and COMP show elevated expression. It has long been known that fenestration of the BM is part of the lesion formation process in psoriasis[68,69] and a soluble form of FN could infiltrate into the epidermis evolving a micro-wound stage.[70,71]

MMPs are also important factors in wound healing; however, they can negatively affect healing if they are not present in the appropriate amount.[72,73] MMP-2 and MMP-9 play a crucial role in wound healing due to their ability to remodel the ECM. The MMP-2 expression is linked with the expression of laminin-332 and increased keratinocyte migration at the edge of acute wounds, while MMP-9 is expressed at the leading edges of migrating keratinocytes during wound closure.[74] During wound healing, MMP-2 and the pro-MMP-2 activator MT1-MMP[59] create a fragment that triggers cell migration by cleaving the gamma-2 chain of laminin-332.[74] In chronic skin wounds, or non-healing wounds, the balance between MMPs and TIMPs is disrupted, which results in a delayed or absent wound closure. In chronic wounds the level of TIMPs are decreased, while the activity of MMPs are upregulated and this imbalance influences the turnover of the ECM.[72] The induction of MMP-2 and MMP-9 occurs via the $\alpha3$ chain of laminin-5.[75] In contrast, elevated MMP-9 is able to suppress the mobility of fibroblasts and keratinocytes[76,77] and this phenomenon can also lead to a delayed re-epithelization.[78]

Recently, we showed that in the psoriatic non-lesional skin, there is an overexpression of keratinocyte growth factor (KGF) and its receptor KGFR (also known as FGFR2), indicating the activation of a wound healing process. Tape stripping of the skin did not lead to any obvious changes in $\alpha5$ integrin, EDA^+FN, KGF or KGFR expression or distribution at 24 and 48 h after tape stripping in non-lesional skin, while in the healthy controls a slight increase in all protein expression was detected based on immunostaining.[48] KGF is known for its effect on keratinocyte proliferation and differentiation, and since it is not present in normal skin, but is induced in wound healing, it is regarded as a major player in the wound healing processes of epithelial tissues.[79] KGF in the skin is produced mainly by fibroblasts, but through the release of IL-1, keratinocytes induce KGF expression and release in fibroblasts.[80] In an *in vitro* co-culture composed of keratinocytes and fibroblasts, Jun and JunB antagonistically regulated the synthesis of fibroblast-derived KGF and GM-CSF.[81] Psoriatic keratinocytes derived from non-lesional epidermis produce significantly higher proinflammatory IL-1 in the presence of IL-17, compared with healthy skin keratinocytes, indicating an intrinsic feature of psoriasis epithelium.[22]

6 | BULLOUS PEMPHIGOID AND PSORIASIS

The coexistence of autoimmune bullous diseases, particularly the anti-laminin-$\gamma1$ (p200) pemphigoid, has been well documented in psoriasis.[82] Autoimmune diseases are characterized by autoantibodies, and autoreactive T cells specific for self-antigens. How exactly they contribute to any given pathological process is not always clear, and some may not play any role in disease pathology, they may only reflect abnormal processes taking place in tissues.[83]

Data indicate that protein complexes that are formed when cells are under stress could possess immunological features that can modulate the host's immune response and induce autoantibody production. In the psoriatic non-lesional tissue, abnormal BM proteins may expose novel epitopes to immune cells and this, together with other immune activating factors, can induce autoantibody formation.[84] It is presently not completely understood how much autoimmunity contributes to psoriasis, and although no particular autoantibody could be linked to the disease so far, one cannot rule out the possibility that autoantibodies may participate in the maintenance of chronic inflammation. Homology between the streptococcal M-protein and keratin 17 raises the possibility of molecular mimicry taking place.[85] Indeed, cross-reactive CD8+ T cells can be detected in patients with psoriasis, especially in patients with HLA-Cw*0602.[86] Circulating LL37-specific T cells correlates with disease activity [16] and ADAMTS-like protein 5 was also proposed in psoriasis as an autoantigen that can contribute to the pathogenesis.[87]

7 | CONCLUSIONS AND PERSPECTIVES

Here, we propose that the seemingly normal looking skin of psoriatic patients represents a balanced, “non-healing-like” micro-wounded

skin phenotype mainly due to its structural abnormalities (Figure 1). Environmental factors (infection, wounding etc.) can easily tip the tissue out of its abnormal, but still visibly balanced state and induce an overt wound reaction (lesional skin). The keratinocyte proliferation rate in the clinically uninvolved epidermis of psoriatic patients is almost the same, as in the healthy epidermis[26] despite the overexpression of KGF and its receptor,[48] but, the psoriatic non-lesional keratinocytes are more sensitive to stress[36] and proliferative signals[21] and the non-lesional skin shows a special para-inflammation state.[37] An intact DEJ region below the basal keratinocytes is crucial to the functional integrity of the skin. Abnormalities of the BM zone within the DEJ will have an effect both on the dermis and the epidermis.[67]

In the psoriatic non-lesional skin, the laminin layer within the BM is disrupted,[41–43] EDA$^+$FN is overexpressed[47,88] and the expression of its receptor, the α5β1 integrin, on the surface of basal keratinocytes is also elevated without any observed hyperproliferation.[39,40] COMP could be one component, which despite these alterations can restrain the proliferation of basal keratinocytes and help to maintain the uninvolved, non-hyperproliferative phenotype of the non-lesional psoriatic skin.[54] MMPs and their inhibitors may play an essential role in the regulation of the ECM proteins in the DEJ region.[56] MMP-2 and MMP-9 overexpression in non-lesional psoriatic skin[14,59] suggest a potential connection with the altered laminin layer within the BM.

Wound healing on surfaces in direct contact with the external environment is tied to innate immune functions, because an intact barrier is essential for defending the body against microbes and other damaging environmental factors. Barrier tissues are highly equipped with numerous machineries to respond to noxa, and as suggested by Matzinger et al., they control immune functions.[89] Barrier dysfunction is not unique to psoriasis; other chronic inflammatory skin diseases are known to have various structural defects in the epidermis. These structural abnormalities may be inherent to the tissue (e.g., mutations in the gene encoding

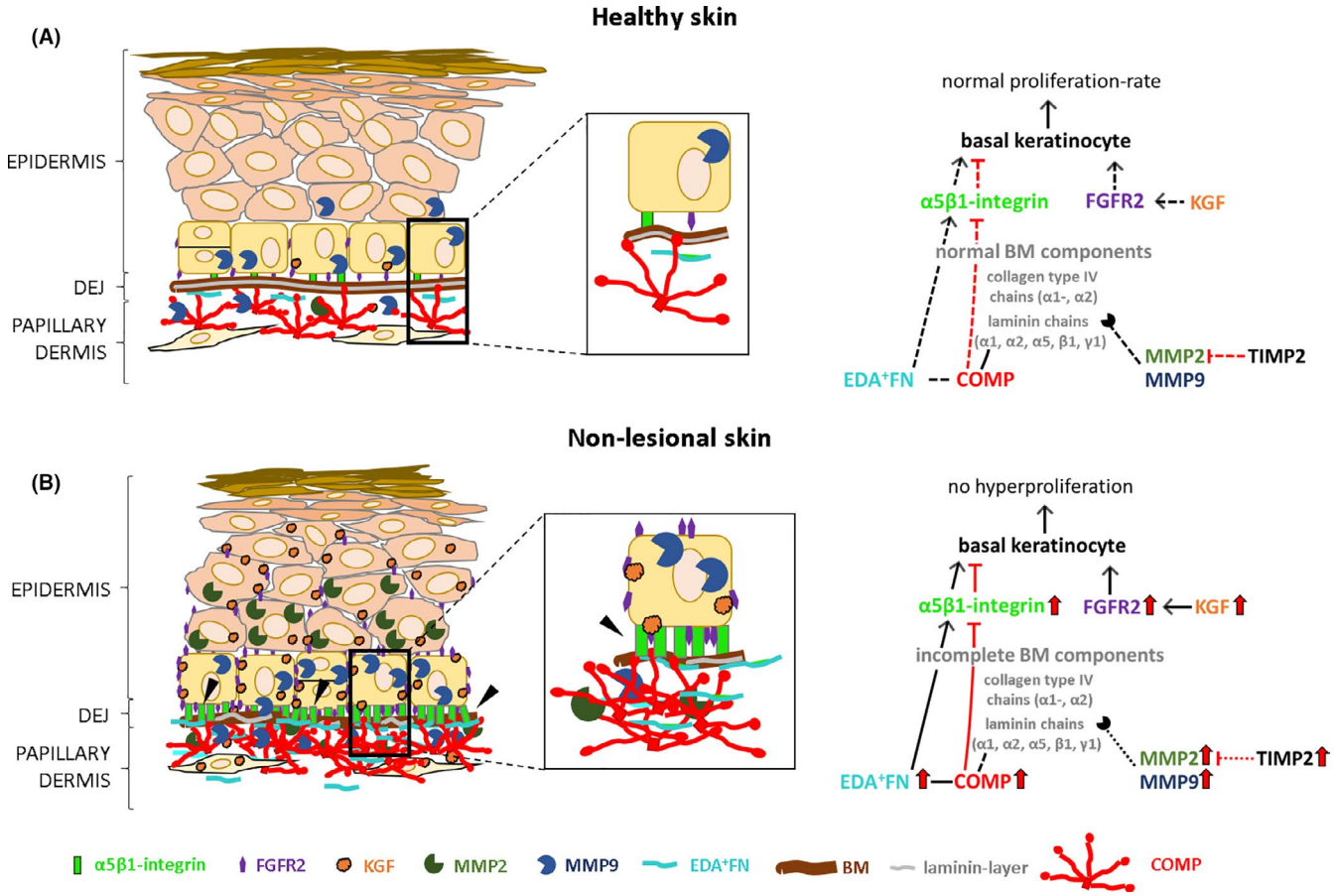

FIGURE 1 Micro-wounds at the dermal-epidermal junction in psoriatic non-lesional skin. Schematic representation of (A) healthy and (B) psoriatic non-lesional skin. The incompleteness of the basement membrane and elevated cartilage oligomeric matrix protein level indicates the "non-healing-like" micro-wounds at the dermal-epidermal junction region of the non-lesional skin. These sites are labelled with black arrowheads. Framed areas show enlarged regions. Straight lines indicate direct, and dashed lines indicate partial relationship between the components. Literature data indicate potential relationship between the dotted line marked components. Red arrows represent the elevated expression of the proteins. (Abbreviations: BM, basement membrane; COMP, cartilage oligomeric matrix protein; DEJ, dermal-epidermal junction; EDA$^+$FN, fibronectin splice variant containing the extra domain A; FGFR2, fibroblast growth factor receptor 2; KGF, keratinocyte growth factor; MMP2, matrix-metalloproteinase 2; MMP9, matrix-metalloproteinase 9; TIMP2, tissue inhibitor of matrix metalloproteinases 2.)

filaggrin in atopic dermatitis)[90] or induced by inflammation (e.g., lichen planus or drug induced reactions where basal keratinocytes are destroyed by cytotoxic T cells).[91] The nature of the barrier dysfunction (e.g., abnormal differentiation of keratinocytes, tight junction, desmosomal, hemi-desmosomal deficiency) and the nature of the dominant inflammation characterize the disease. For example, data suggest that atopic dermatitis is primarily an IL-13 dominant disease, while in psoriasis the dominant immune reaction is polarized towards the IL-17 response.[92] In the chronic phase of inflammation common features of the wound healing immune response may be seen, such as in atopic dermatitis, where in the chronic phase of the disease a prominent activation of skin barrier repair signature can be detected in transcriptomic profiling using RNA-sequencing.[93]

Understanding the contribution of the tissue factors in the pathomechanism of psoriasis will be essential to design therapies that give longer term relief from the disease than presently available treatments.

If, as indicated by our current knowledge, psoriasis is indeed genetically determined, the non-lesional tissue is the place to look for the primary effects of the inherent susceptibility factors. In future studies of the non-lesional psoriatic tissue, it will be important to better characterize the investigated tissue samples. HLA-Cw*0602 association, previous lesional versus never lesional status and severity of the disease based on PASI scores may influence the structural changes and its importance in disease pathophysiology.

ACKNOWLEDGEMENTS

We are grateful to all of the volunteers who provided us skin samples during the previous studies and to our colleagues who participated in our psoriasis research projects.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

ZBC and RB have made substantial contributions to conception. ZBC, RB, LBF, NB and BG involved in drafting the manuscript. ZBC, MS and LK involved in revising critically for important intellectual content and given final approval of the version to be published. All authors have read and approved the final manuscript.

ORCID

Renáta Bozó https://orcid.org/0000-0003-4242-2474

REFERENCES

1. Nickoloff BJ, Qin J-Z, Nestle FO. Immunopathogenesis of psoriasis. *Clin Rev Allergy Immunol*. 2007;33(1-2):45-56.
2. Meier M, Sheth PB. Clinical spectrum and severity of psoriasis. *Curr. Probl. Dermatol*. 2009;38:1-20.
3. Menter A. Psoriasis and psoriatic arthritis overview. *Am J Manag Care*. 2016;22(8 Suppl):s216-s224.
4. Ocampo D V, Gladman D. Psoriatic arthritis. *F1000Research*. 2019;8:1665.
5. Oliveira MdFSPd, Rocha BDO, Duarte GV. Psoriasis: classical and emerging comorbidities. *An Bras Dermatol*. 2015;90(1):9-20.
6. Yan D, Afifi L, Jeon C, Cordoro KM, Liao W. A cross-sectional study of psoriasis triggers among different ethno-racial groups. *J Am Acad Dermatol*. 2017;77(4):756-758.e1.
7. Twelves S, Mostafa A, Dand N, et al. Clinical and genetic differences between pustular psoriasis subtypes. *J Allergy Clin Immunol*. 2019;143(3):1021-1026. https://doi.org/10.1016/j.jaci.2018.06.038
8. Chen L, Tsai T-F. HLA-Cw6 and psoriasis. *Br J Dermatol*. 2018;178(4):854-862.
9. Lowes MA, Bowcock AM, Krueger JG. Pathogenesis and therapy of psoriasis. *Nature*. 2007;445(7130):866-873.
10. Cafaro G, McInnes IB. Psoriatic arthritis: tissue-directed inflammation? *Clin Rheumatol*. 2018;37(4):859-868.
11. Pasquali L, Srivastava A, Meisgen F, et al. The keratinocyte transcriptome in psoriasis: pathways related to immune responses, cell cycle and keratinization. *Acta Derm Venerol*. 2019;99(2):196-205.
12. Kadunce DP, Krueger GG. Pathogenesis of psoriasis. *Dermatol Clin*. 1995;13(4):723-737.
13. Szél E, Bozó R, Hunyadi E, et al. Comprehensive proteomic analysis reveals intermediate stage of non-lesional psoriatic skin and points out the importance of proteins outside this trend. *Sci Rep*. 2019;9(1):11382.
14. Chiricozzi A, Suárez-Fariñas M, Fuentes-Duculan J, et al. Increased expression of interleukin-17 pathway genes in nonlesional skin of moderate-to-severe psoriasis vulgaris. *Br J Dermatol*. 2016;174(1):136-145.
15. Swindell WR, Remmer HA, Sarkar MK, et al. Proteogenomic analysis of psoriasis reveals discordant and concordant changes in mRNA and protein abundance. *Genome Med*. 2015;7(1):86.
16. Lande R, Botti E, Jandus C, et al. The antimicrobial peptide LL37 is a T-cell autoantigen in psoriasis. *Nat Commun*. 2014;5(1):5621.
17. Cai Y, Shen X, Ding C, et al. Pivotal role of dermal IL-17-producing γδ T cells in skin inflammation. *Immunity*. 2011;35(4):596-610.
18. Gray EE, Suzuki K, Cyster JG. Cutting edge: Identification of a motile IL-17-producing gammadelta T cell population in the dermis. *J. Immunol*. 2011;186(11):6091-6095.
19. O'Brien RL, Born WK. Dermal γδ T cells–What have we learned? *Cell. Immunol*. 2015;296(1):62-69.
20. Chiricozzi A, Nograles KE, Johnson-Huang LM, et al. IL-17 induces an expanded range of downstream genes in reconstituted human epidermis model. *PLoS One*. 2014;9(2):e90284.
21. Bata-Csorgo Z, Hammerberg C, Voorhees JJ, Cooper KD. Kinetics and regulation of human keratinocyte stem cell growth in short-term primary ex vivo culture. Cooperative growth factors from psoriatic lesional T lymphocytes stimulate proliferation among psoriatic uninvolved, but not normal, stem keratinocytes. *J Clin Invest*. 1995;95(1):317-327.
22. Muhr P, Zeitvogel J, Heitland I, Werfel T, Wittmann M. Expression of interleukin (IL)-1 family members upon stimulation with IL-17 differs in keratinocytes derived from patients with psoriasis and healthy donors. *Br J Dermatol*. 2011;165(1):189-193.
23. Cheuk S, Wikén M, Blomqvist L, et al. Epidermal Th22 and Tc17 cells form a localized disease memory in clinically healed psoriasis. *J Immunol*. 2014;192(7):3111-3120.
24. Gallais Sérézal I, Hoffer E, Ignatov B, et al. A skewed pool of resident T cells triggers psoriasis-associated tissue responses in never-lesional skin from patients with psoriasis. *J Allergy Clin Immunol*. 2019;143(4):1444-1454.
25. Weiss G, Shemer A, Trau H. The Koebner phenomenon: review of the literature. *J Eur Acad Dermatol Venereol*. 2002;16(3):241-248.
26. Wiley HE, Weinstein GD. Abnormal proliferation of uninvolved psoriatic epidermis: differential induction by saline, propranolol, and tape stripping in vivo. *J Invest Dermatol*. 1979;73(6):545-547.

27. Hatta N, Takata M, Kawara S, Hirone T, Takehara K. Tape stripping induces marked epidermal proliferation and altered TGF-alpha expression in non-lesional psoriatic skin. *J Dermatol Sci*. 1997;14(2):154-161.
28. Sonkoly E, Bata-Csorgo Z, Pivarcsi A, et al. Identification and characterization of a novel, psoriasis susceptibility-related noncoding RNA gene, PRINS. *J Biol Chem*. 2005;280(25):24159-24167.
29. Danis J, Göblös A, Bata-Csörgő Z, Kemény L, Széll M. PRINS non-coding RNA regulates nucleic acid-induced innate immune responses of human keratinocytes. *Front Immunol*. 2017;8:1053.
30. Szegedi K, Sonkoly E, Nagy N, et al. The anti-apoptotic protein G1P3 is overexpressed in psoriasis and regulated by the non-coding RNA, PRINS. *Exp Dermatol*. 2010;19(3):269-278.
31. Hanisch C, Sharbati J, Kutz-Lohroff B, Huber O, Einspanier R, Sharbati S. TFF3-dependent resistance of human colorectal adenocarcinoma cells HT-29/B6 to apoptosis is mediated by miR-491-5p regulation of lncRNA PRINS. *Cell Death Discov*. 2017;3:16106.
32. Szegedi K, Göblös A, Bacsa S, et al. Expression and functional studies on the noncoding RNA, PRINS. *Int J Mol Sci*. 2013;14(1):205-225.
33. Yu T-M, Palanisamy K, Sun K-T, et al. RANTES mediates kidney ischemia reperfusion injury through a possible role of HIF-1α and LncRNA PRINS. *Sci Rep*. 2016;6(1):18424.
34. Széll M, Danis J, Bata-Csörgő Z, Kemény L. PRINS, a primate-specific long non-coding RNA, plays a role in the keratinocyte stress response and psoriasis pathogenesis. *Pflugers Arch*. 2016;468:935-943.
35. Göblös A, Danis J, Vas K, Bata-Csörgő Z, Kemény L, Széll M. Keratinocytes express functional CARD18, a negative regulator of inflammasome activation, and its altered expression in psoriasis may contribute to disease pathogenesis. *Mol Immunol*. 2016;73:10-18.
36. Szabó K, Bata-Csörgő Z, Dallos A, et al. Regulatory networks contributing to psoriasis susceptibility. *Acta Derm Venereol*. 2014;94(4):380-385.
37. Medzhitov R. Origin and physiological roles of inflammation. *Nature*. 2008;454(7203):428-435.
38. Wang Y, Edelmayer R, Wetter J, et al. Monocytes/Macrophages play a pathogenic role in IL-23 mediated psoriasis-like skin inflammation. *Sci Rep*. 2019;9(1):5310.
39. Pellegrini G, De Luca M, Orecchia G, et al. Expression, topography, and function of integrin receptors are severely altered in keratinocytes from involved and uninvolved psoriatic skin. *J Clin Invest*. 1992;89(6):1783-1795.
40. Bata-Csorgo Z, Cooper KD, Ting KM, Voorhees JJ, Hammerberg C. Fibronectin and alpha5 integrin regulate keratinocyte cell cycling. A mechanism for increased fibronectin potentiation of T cell lymphokine-driven keratinocyte hyperproliferation in psoriasis. *J Clin Invest*. 1998;101(7):1509-1518.
41. Mondello MR, Magaudda L, Pergolizzi S, et al. Behaviour of laminin 1 and type IV collagen in uninvolved psoriatic skin. Immunohistochemical study using confocal laser scanning microscopy. *Arch Dermatol Res*. 1996;288(9):527-531.
42. Vaccaro M, Magaudda L, Cutroneo G, et al. Changes in the distribution of laminin alpha1 chain in psoriatic skin: immunohistochemical study using confocal laser scanning microscopy. *Br J Dermatol*. 2002;146(3):392-398.
43. Fleischmajer R, Kuroda K, Utani A, et al. Differential expression of laminin alpha chains during proliferative and differentiation stages in a model for skin morphogenesis. *Matrix Biol*. 2000;19(7):637-647.
44. Ho T-C, Yeh S-I, Chen S-L, Tsao Y-P. The psoriasis therapeutic potential of a novel short laminin peptide C16. *Int J Mol Sci*. 2019;20(13):3144.
45. To WS, Midwood KS. Plasma and cellular fibronectin: distinct and independent functions during tissue repair. *Fibrogenesis Tissue Repair*. 2011;4:21.
46. Kornblihtt AR, Pesce CG, Alonso CR, et al. The fibronectin gene as a model for splicing and transcription studies. *FASEB J*. 1996;10(2):248-257.
47. Széll M, Bata-Csörgő Z, Koreck A, et al. Proliferating keratinocytes are putative sources of the psoriasis susceptibility-related EDA+ (extra domain A of fibronectin) oncofetal fibronectin. *J Invest Dermatol*. 2004;123(3):537-546.
48. Gubán B, Vas K, Balog Z, et al. Abnormal regulation of fibronectin production by fibroblasts in psoriasis. *Br J Dermatol*. 2016;174(3):533-541.
49. Madonna S, Scarponi C, Sestito R, Pallotta S, Cavani A, Albanesi C. The IFN-gamma-dependent suppressor of cytokine signaling 1 promoter activity is positively regulated by IFN regulatory factor-1 and Sp1 but repressed by growth factor independence-1b and Krüppel-like factor-4, and it is dysregulated in psoriatic keratinocytes. *J Immunol*. 2010;185(4):2467-2481.
50. McKenzie RC, Sabin E. McKenzie RC, Sabin E. Aberrant signalling and transcription factor activation as an explanation for the defective growth control and differentiation of keratinocytes in psoriasis: a hypothesis. *Exp Dermatol*. 2003;12(4):337-345.
51. Okamura Y, Watari M, Jerud ES, et al. The extra domain A of fibronectin activates Toll-like receptor 4. *J Biol Chem*. 2001;276(13):10229-10233.
52. Leask A, Abraham DJ. TGF-beta signaling and the fibrotic response. *FASEB J*. 2004;18(7):816-827.
53. White ES, Baralle FE, Muro AF. New insights into form and function of fibronectin splice variants. *J Pathol*. 2008;216(1):1-14.
54. Bozó R,Szél E, Danis J, et al. Cartilage oligomeric matrix protein negatively influences keratinocyte proliferation via α5β1-Integrin: potential relevance of altered cartilage oligomeric matrix protein expression in psoriasis. *J Invest Dermatol*. 2020;140(9):1733-1742.e7.
55. Agarwal P, Zwolanek D, Keene DR, et al. Collagen XII and XIV, new partners of cartilage oligomeric matrix protein in the skin extracellular matrix suprastructure. *J Biol Chem*. 2012;287(27):22549-22559.
56. Mezentsev A, Nikolaev A, Bruskin S. Matrix metalloproteinases and their role in psoriasis. *Gene*. 2014;540(1):1-10.
57. Birkedal-Hansen H. Proteolytic remodeling of extracellular matrix. *Curr Opin Cell Biol*. 1995;7(5):728-735.
58. Shipley JM,Doyle GA, Fliszar CJ, et al. The structural basis for the elastolytic activity of the 92-kDa and 72-kDa gelatinases. Role of the fibronectin type II-like repeats. *J Biol Chem*. 1996;271(8):4335-4341.
59. Fleischmajer R, Kuroda K, Hazan R, et al. Basement membrane alterations in psoriasis are accompanied by epidermal overexpression of MMP-2 and its inhibitor TIMP-2. *J Invest Dermatol*. 2000;115(5):771-777.
60. Morhenn VB, Nelson TE, Gruol DL. The rate of wound healing is increased in psoriasis. *J Dermatol Sci*. 2013;72(2):87-92.
61. Lai Y, Li D, Li C, et al. The antimicrobial protein REG3A regulates keratinocyte proliferation and differentiation after skin injury. *Immunity*. 2012;37(1):74-84.
62. Nickoloff BJ, Bonish BK, Marble DJ, et al. Lessons learned from psoriatic plaques concerning mechanisms of tissue repair, remodeling, and inflammation. *J Investig Dermatol Symp Proc*. 2006;11(1):16-29.
63. Jakhu H, Gill G, Singh A. Role of integrins in wound repair and its periodontal implications. *J Oral Biol Craniofac Res*. 2018;8(2):122-125.
64. Muro AF, Chauhan AK, Gajovic S, et al. Regulated splicing of the fibronectin EDA exon is essential for proper skin wound healing and normal lifespan. *J Cell Biol*. 2003;162(1):149-160.
65. Grinnell F, Toda K, Takashima A. Activation of keratinocyte fibronectin receptor function during cutaneous wound healing. *J Cell Sci Suppl*. 1987;8:199-209.
66. Agarwal P, Schulz J-N, Blumbach K, et al. Enhanced deposition of cartilage oligomeric matrix protein is a common feature in fibrotic skin pathologies. *Matrix Biol*. 2013;32(6):325-331.

67. Fisher G, Rittié L. Restoration of the basement membrane after wounding: a hallmark of young human skin altered with aging. *J Cell Commun Signal*. 2018;12(1):401-411.
68. Heng MC, Kloss SG, Kuehn CS, Chase DG. Significance and pathogenesis of basal keratinocyte herniations in psoriasis. *J Invest Dermatol*. 1986;87(3):362-366.
69. Pinkus H, Mehregan AH. The primary histologic lesion of seborrheic dermatitis and psoriasis. *J Invest Dermatol*. 1966;46(1):109-116.
70. Fyrand O. Studies on fibronectin in the skin. II. Indirect immunofluorescence studies in psoriasis vulgaris. *Arch Dermatol Res*. 1979;266(1):33-41.
71. Verschoore M, Kowalewski C, Chorzelska MJ, Bernard BA, Darmon YM. Intraepidermal leakage of plasma proteins after tape stripping of normal skin and uninvolved psoriatic skin. *Br J Dermatol*. 1990;122(3):391-397.
72. Martins VL, Caley M, O'Toole EA. Matrix metalloproteinases and epidermal wound repair. *Cell Tissue Res*. 2013;351(2):255-268.
73. Menke MN, Menke NB, Boardman CH, Diegelmann RF. Biologic therapeutics and molecular profiling to optimize wound healing. *Gynecol Oncol*. 2008;111(2):S87-S91.
74. Caley MP, Martins VLC, O'Toole EA. Metalloproteinases and wound healing. *Adv Wound Care*. 2015;4(4):225-234.
75. Momota Y, Suzuki N, Kasuya Y, et al. Lamininα3 LG4 module induces keratinocyte migration: involvement of matrix metalloproteinase-9. *J Recept Signal Transduction*. 2005;25(1):1-17.
76. Reiss MJ, Han Y-P, Garcia E, Goldberg M, Yu H, Garner WL. Matrix metalloproteinase-9 delays wound healing in a murine wound model. *Surgery*. 2010;147(2):295-302.
77. Xue S-N, Lei J, Yang C, Lin D-Z, Yan L. The biological behaviors of rat dermal fibroblasts can be inhibited by high levels of MMP9. *Exp Diabetes Res*. 2012;2012:1-7.
78. Kyriakides TR, Wulsin D, Skokos EA, et al. Mice that lack matrix metalloproteinase-9 display delayed wound healing associated with delayed reepithelization and disordered collagen fibrillogenesis. *Matrix Biol*. 2009;28(2):65-73.
79. Yen TTH, Thao DTP, Thuoc TL. An overview on keratinocyte growth factor: from the molecular properties to clinical applications. *Protein Pept Lett*. 2014;21(3):306-317.
80. Chedid M, Rubin JS, Csaky KG, Aaronson SA. Regulation of keratinocyte growth factor gene expression by interleukin 1. *J Biol Chem*. 1994;269(14):10753-10757.
81. Szabowski A, Maas-Szabowski N, Andrecht S, et al. c-Jun and JunB antagonistically control cytokine-regulated mesenchymal–epidermal interaction in skin. *Cell*. 2000;103(5):745-755.
82. Ohata C, Ishii N, Koga H, et al. Coexistence of autoimmune bullous diseases (AIBDs) and psoriasis: a series of 145 cases. *J Am Acad Dermatol*. 2015;73(1):50-55.
83. Eggleton P. Stress protein-polypeptide complexes acting as autoimmune triggers. *Clin Exp Immunol*. 2003;134(1):6-8.
84. Gál B, Dulic S, Kiss M, et al. Increased circulating anti-α6-integrin autoantibodies in psoriasis and psoriatic arthritis but not in rheumatoid arthritis. *J Dermatol*. 2017;44(4):370-374.
85. Valdimarsson H, Thorleifsdottir RH, Sigurdardottir SL, Gudjonsson JE, Johnston A. Psoriasis–as an autoimmune disease caused by molecular mimicry. *Trends Immunol*. 2009;30(10):494-501.
86. Liang Y, Sarkar MK, Tsoi LC, Gudjonsson JE. Psoriasis: a mixed autoimmune and autoinflammatory disease. *Curr Opin Immunol*. 2017;49:1-8.
87. Arakawa A,Siewert K, Stöhr J, et al. Melanocyte antigen triggers autoimmunity in human psoriasis. *J Exp Med*. 2015;212(13):2203-2212.
88. Ting KM, Rothaupt D, McCormick TS, et al. Overexpression of the oncofetal Fn variant containing the EDA splice-in segment in the dermal-epidermal junction of psoriatic uninvolved skin. *J Invest Dermatol*. 2000;114(4):706-711.
89. Matzinger P, Kamala T. Tissue-based class control: the other side of tolerance. *Nat Rev Immunol*. 2011;11(3):221-230.
90. Palmer CNA,Irvine AD, Terron-Kwiatkowski A, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. *Nat Genet*. 2006;38(4):441-446.
91. Ammar M, Mokni M, Boubaker S, El Gaied A, Ben Osman A, Louzir H. Involvement of granzyme B and granulysin in the cytotoxic response in lichen planus. *J Cutan Pathol*. 2008;35(7):630-634.
92. Tsoi LC,Rodriguez E, Degenhardt F, et al. Atopic dermatitis is an IL-13-dominant disease with greater molecular heterogeneity compared to psoriasis. *J Invest Dermatol*. 2019;139(7):1480-1489.
93. Tsoi LC,Rodriguez E, Stölzl D, et al. Progression of acute-to-chronic atopic dermatitis is associated with quantitative rather than qualitative changes in cytokine responses. *J Allergy Clin Immunol*. 2020;145(5):1406-1415.

How to cite this article: Bozó R, Flink LB, Belső N, et al. Could basement membrane alterations, resembling microwounds at the dermo-epidermal junction in psoriatic non-lesional skin, make the skin susceptible to lesion formation?. *Exp Dermatol*. 2021;00:1–8. https://doi.org/10.1111/exd.14267